REMARKS

The paragraph starting on page 8, line 21 of the specification has been amended to correct obvious punctuation and syntax errors. No new matter is added.

Claims 54 and 60-68 are currently pending in the application. Applicants have amended claim 54 to recite "post-partum mammalian" as a modifier of "placenta." No new matter is added by this amendment, as the specification is directed to a post-partum mammalian placenta. Support for this amendment is found at least at page 7, lines 21-33; and page 26, line 20 to page 27, line 25. New claim 69 is added. Support for this claim is found at least on page 21, lines 8-15 and page 26, lines 20-33. Upon entry of the present amendment, claims 54 and 60-69 will be pending. Applicant reserves the right to claim and prosecute any presently unclaimed subject matter in the instant specification in this or a related application.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 54 and 60-68 under 35 U.S.C. § 112, second paragraph as indefinite in the recitation of "a cell which is neither maternal nor fetal in origin." Applicants traverse.

The Examiner contends that because "all cells in a mammalian subject [] originated from a fetus in the uterus of a mother, it is unclear what type of cells the instant claim encompasses or excludes . . ." Office Action at page 12. The word "origin" means "the point at which something comes into existence *or from which it is derived* . . ." (*see, e.g.*, THE AMERICAN HERITAGE COLLEGE DICTIONARY, THIRD EDITION, Houghton Mifflin Co., Boston, at page 963 (1997)) (emphasis added). "Origin" in the claims is used to indicate the point from which the cell is derived, not its ontogeny. The terms "fetal" and "maternal" clearly identify to persons of skill in the art the origin of a particular cell. For example, "fetal" means "of, relating to, characteristic of or being a fetus" (*id.* at page 504) and "maternal" means "relating to or characteristic of a mother . . ." (*id.* at page 837). Thus, "a cell that is not fetal or maternal in origin" would mean, to a person of skill in the art, a cell that is not obtained from a fetus, or the mother of that fetus, respectively. Conversely, the phrase would mean a mammalian cell taken from any other source, *e.g.*, an adult related to the mother and fetus; an adult unrelated to the mother and fetus; a placenta; etc. Thus, claim 54, and claims dependent from claim 54, are not indefinite on this basis. Applicant therefore requests that the Examiner withdraw the rejection of claims 54 and 60-68 on this basis.

The Examiner has also rejected claim 60 under 35 U.S.C. § 112, second paragraph as indefinite in the recitation of "the isolated mammalian placenta" because the claim lacks

sufficient antecedent basis. Applicant has amended claim 54 to recite "mammalian placenta," providing such antecedent basis. Applicant requests that the Examiner withdraw the rejection of claims 54 and 60-68 on this basis.

The Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 54 and 60-68 under 35 U.S.C. § 112, first paragraph as allegedly nonenabled.[1] Because the Examiner has not made out a sufficient *prima* facie case of nonenablement, Applicant traverses. Applicant has amended claim 54 to recite that the isolated placenta is a *mammalian* placenta, and that the placenta comprises a *mammalian* cell that is neither fetal nor maternal in origin.

The Examiner's assertion of nonenablement of the claims is legally insufficient because (1) the Examiner appears to overlook teachings of the specification that support enablement; (2) in many cases, the Examiner turns first to the *art* to identify potential issues rather than first examining the teachings of the specification and determining whether one of skill in the art could practice the invention as claimed and described; (3) most of the art cited by the Examiner is not relevant to a placenta containing a cell not obtained from that placenta; (4) the Examiner asserts at least one improper standard for judging enablement; and (5) the Examiner makes several unsupported claims of nonenablement.

The Examiner first overlooks teachings within the present specification regarding preparation of the placenta for seeding. In particular, the Examiner faults the specification for purportedly failing to teach "how to deplete endogenous cells to provide bedding for the exogenous cells, how to uniformly seed the exogenous cells in such a complicated structure, and how to deliver nutrients to the seeded cells and the perfused placenta, how to monitor the growth and differentiation of the seeded cells, and how to harvest the propagated cells." Office Action, page 5. The specification teaches how to deplete endogenous cells at page 27, lines 2-12; such methods are also well-known by virtue of at least one publication. *See, e.g.*, United States Application Publication 2002/0160510 "Renovation and Repopulation of Decellularized Tissues and Cadaveric Organs by Stem Cells." The law is clear that such known techniques need not be included in the specification. *See, e.g.*, M.P.E.P. 2164.05(a) and references cited therein. Delivery of the cells may be accomplished by perfusion or

[1] Applicant first points out that this is the first time the Examiner has raised nonenablement as a basis of rejection, despite the fact that a substantially similar claim was originally-filed (*e.g.*, claim 54). The Examiner is required to avoid piecemeal examination. *See* 37 C.F.R. 1.104(b) ("The examiner's action shall be complete as to all matters . . .") (requiring an enablement rejection in the first office action if deemed appropriate); *see* also Manual of Patent Examining Procedure ("MPEP") 707.07(g). This delay is particularly troubling in light of the 20-year limitation on the term of any patent that would issue from this application, as provided by 35 U.S.C. § 154(2); M.P.E.P. 2164.04. Applicants should have had the opportunity to address this rejection in the first Office Action of August 28, 2003.

injection. Specification, page 27, first paragraph. Delivery of nutrients to the seeded cells is accomplished by perfusion. *See, e.g.*, specification, page 17, lines 19-24. Harvesting or collecting the propagated cells is described at least on pages 19-20 of the specification. The specification is therefore hardly "silent" about such aspects of the invention.

The Examiner also cites art not to describe the state of the art, according to *In re Wands*, but to establish a purported set of criteria for enablement. No such set of criteria exists in the art, however. Moreover, most of the cited art is irrelevant. For example, the Examiner cites Kleinman *et al.* U.S. Patent No. 4,829,000, particularly col. 4, lines 16-21, to support the Examiner's proposition that the human placenta "does not appear to have immune privilege." Office Action, page 9. Kleinman allegedly discloses the use of placental tissue *in vivo* - in an individual with an active immune system. Kleinman discloses nothing about immune interactions between an isolated placenta and an exogenous cell. In fact, there would be no immune reactions, because neither have active immune systems. Kleinman, therefore, is irrelevant to the pending claims.

The Examiner further argues that Oppenheim *et al.*, *Theriogenology* 55:1567-81 (2001) shows that "the immune reaction of the placenta causes pregnancy failure in sheep-goat interspecies hybrid pregnancy . . . [and thus] it is unknown whether allogeneic and xenogenic cells are compatible with human placenta substances, and would sufficiently grow in mammalian placenta, and whether any animal cells would grow in a human term placenta." Office Action, page 9. Oppenheim discloses nothing about the "immune reaction of the placenta," suggesting only that certain placentas in that study developed non-normally. Like Kleinman, Oppenheim allegedly discloses a placenta *in vivo*, in an individual with a functioning immune system, but fails to teach any interaction between a placenta and a cell *in vitro*. This alleged teaching is irrelevant to whether a cell seeded into an isolated mammalian placenta would grow there. Therefore, Oppenheim, like Kleinman, is irrelevant to an analysis of whether an isolated placenta comprising a non-placental cell is enabled.

The Examiner further contends that certain prior art references mandate a "size limitation" in placenta organ culture, citing Stromberg *et al.*, *Meth. Cell. Biol.* 21:227-252 (1980) ("Stromberg"), Ma *et al.*, *Tissue Eng.* 5(2):91-102 (1999) ("Ma") and Contractor *et al.*, *Cell. Tiss. Res.* 237:609-617 (1984) ("Contractor"). Stromberg, in particular the portion to which the Examiner refers, purportedly teaches the tissue culture of small parts of a mammalian placenta. Nothing in Stromberg suggests that tissue necrosis or similar problems would be experienced in the perfusion of a complete placenta through the placenta's vasculature, as taught in the instant specification. Stromberg is therefore irrelevant in assessing the enablement of the current claims. The Examiner cites Ma simply for the

proposition that placental trophoblast cells are expected to live in tissue culture for only ~7 days, but fails to explain how this alleged disclosure demonstrates nonenablement. In fact, it does not, for nowhere does the instant specification, or the art, require that the placenta be perfused for seven or more days in order for a person of skill in the art to be able to practice the claimed invention. Moreover, the citation of Ma fails to take into account the difference in behavior of cultured trophoblasts, taught in Ma, compared to trophoblasts in the placenta of the instant specification. A person of skill in the art would know that cells in tissue culture do not behave, propagate and survive as do cells in an organ, their natural environment. Finally, Contractor purportedly teaches only the culture of placental lobules, not whole placentas, and does not teach that a placenta could not be used as a bioreactor for several days. None of these references teaches anything about the suitability of the placenta for exogenous cell culture. In sharp contrast, Sanders *et al.*, U.S. Patent No. 3,862,002, which the Examiner does not take into account, appears to relate that placental culture for several days is feasible.[2] The Examiner fails to address this discrepancy.

The Examiner also asserts legally insufficient standards to reject the claims for nonenablement. For example, the Examiner contends that "[t]he specification fails to teach whether and why it is [advantageous] to culture the stem cells in the perfused placenta compared to the culture dish routinely used by the skilled in the art." Office Action, page 10. Relative advantage of a claimed invention over previous teachings is not a standard for enablement stated in the patent laws, Code of Federal Regulations, or the Manual of Patent Examining Procedure. To reiterate, the Examiner must explain why the invention as claimed could not be *practiced* without *undue experimentation. See* M.P.E.P. 2143 *et seq.* The Examiner is not allowed to base a finding of nonenablement on ostensibly missing statements of how the invention is superior to other methods in the art.

The Examiner also faults the specification for failing to teach "how to uniformly seed the exogenous cells in such a complicated structure. . ." Office Action, page 5. *Uniformity* of seeding is irrelevant to enablement, because the neither the claims nor the invention as described, nor the cited art, require "*uniform*" seeding of the exogenous cells. Certainly, the law does not demand it. "[T]he patent document is not intended to be a production specification." *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931 (Fed. Cir. 1990). "Uniformity" is thus not a legally-sufficient standard for enablement.

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[2] The Examiner has cited Sanders, U.S. Patent No. 3,862,002 as part of a rejection of certain of the currently-pending claims as obvious under 35 U.S.C. § 103 (Office Action, page 14). The Examiner there cites Sanders as teaching perfusion of a placenta for days at a time. References cited as prior art are presumed to be enabled. M.P.E.P. 2121. As such, the Examiner in this Office action argues both that placental perfusion is feasible and is not feasible. The Examiner cannot have it both ways; either the Examiner believes perfusion of a placenta for an extended time to be possible or believes it not to be possible.

Finally, the Examiner makes several unsupported claims of nonenablement. For example, the Examiner contends that "it is unknown and the specification fails to teach whether the [decellularized] placenta still can support the propagation of stem cells once it is detached from the uterus and has been made cell free," and that the claimed placenta is thus not enabled. Office Action, pages 9-10. The Examiner provides absolutely no support for this assertion. Applicant has taught how to make and use the claimed invention, and nothing more is required for enablement. If the Examiner doubts the operability of the invention, the Examiner must provide a declaration in support; merely contending such is not sufficient. Moreover, a reference cited by the Examiner, Tseng *et al.*, U.S. Patent No. 6,326,019, allegedly relates that "the supporting power of the placenta material is not dependent upon living cells but [is] mediated by the amniotic matrix . . ." Office Action, page 8, lines 6-8. The Examiner's contention is therefore without basis.

Thus, the specification teaches one of skill in the art how to obtain, culture and perfuse a placenta, and how to culture exogenous cells within it. Absent reasonable *evidence* to the contrary, the Examiner must accept the specification's teaching of the manner of making and using the invention as enabling. M.P.E.P. 2164.04. The Examiner has not made out the requisite *prima facie* case of nonenablement because the Examiner has not adequately explained why one of skill in the art would be required to engage in *undue* experimentation in order to practice the claimed invention. The art cited by the Examiner does not support the Examiner's contentions, and, in many cases, is simply irrelevant to the claims at issue. Applicant therefore requests that the Examiner withdraw the rejection of claims 54 and 60-68 on this basis.

The Rejections Under 35 U.S.C. § 102(b)/103(a) Should Be Withdrawn

The Examiner has rejected claims 54 and 68 under 35 U.S.C. § 102(b) as anticipated by, or in the alternative, under 103(a) as obvious over, MacLaren *et al., J. Comp. Pathol.* 106:279-297 (1992) ("MacLaren"). Applicant traverses.

For a reference to anticipate, the reference must disclose each and every limitation of the claim to which it is compared. *Schumer v. Laboratory Computer Sys., Inc.*, 308 F.3d 1304 (Fed. Cir. 2002); *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292 (Fed. Cir. 2002).

Obviousness under 35 U.S.C. § 103(a) requires a determination that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 U.S. 1 (1966). The relevant inquiry is whether the prior

art suggests the invention and whether the prior art provides one of ordinary skill in the art a reasonable expectation of success in practicing the claimed invention. Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998). Applicant has amended claim 54 to recite that the placenta is a "post-partum" placenta, *i.e.*, a placenta without a fetus.

Claims 54 and 68 are neither anticipated by, nor obvious over, MacLaren because MacLaren does not teach a *post-partum* placenta comprising a *cell that is not fetal or maternal in origin*. First, a post-partum placenta contains no fetus, and thus contains no exogenous cells (that is, cells derived from a source other than the mother or fetus). Moreover, even the pre-partum placenta taught by MacLaren does not contain exogenous cells. The Examiner contends that "MacLaren et al. teach an interspecies goat placenta comprising sheep cells which are neither maternal nor fetal in origin (e.g., abstract and table 1). Office Action, page 13. In fact, MacLaren allegedly teaches the implantation of a sheep embryo into a goat, and a goat embryo into a sheep (*see*, *e.g.*, Abstract, Methods, Table 1). In both cases, the fetus and placenta are of the same species. The Examiner appears to assume that a sheep fetus carried by a goat constitutes "sheep cells which are neither maternal nor fetal in origin . . ." However, all cells of a fetus are demonstrably "fetal in origin." It makes no difference, in the context of claims 54 and 68, whether the fetus is of a different species than the mother carrying it. It is still a fetus, and its cells are fetal cells. In any event, as noted above, the *post-partum* placenta allegedly disclosed in MacLaren contains no non-fetal, non-maternal cell.

MacLaren further does not teach a *bloodless* placenta. The Examiner contends that "it is noted that the rinse would wash out at least most of the blood cells," Office Action, page 14, and that the placenta disclosed in MacLaren is thus the same as the claimed placenta because perfusion would only rinse away any remaining cord blood in the placenta. *Id.* The Examiner provides no support for this contention; it is therefore speculation and not sufficient to demonstrate anticipation. In fact, rinsing the placenta as taught by MacLaren (page 281, third paragraph) would not render the placenta bloodless, because rinsing would not remove blood from the placenta's vasculature. MacLaren does not even teach that the placentas are exsanguinated, much less that all blood is removed. MacLaren thus fails to teach or suggest a bloodless placenta.

Because MacLaren fails to teach a *post-partum*, *bloodless* placenta comprising a *cell which is neither fetal nor maternal in origin*, MacLaren fails to anticipate claims 54 and 68.

MacLaren further does not render the subject matter of claims 54 and 68 obvious. The Examiner has not explained how the claimed placenta is obvious over the placentas shown in MacLaren. The Examiner has thus not made out a *prima facie* case of obviousness. Moreover, because MacLaren purportedly teaches that the placentas are only weighed and sampled for histological studies, a person of ordinary skill in the art would not be motivated to perfuse and culture those placentas to arrive at the placenta of claims 54 and 68. Moreover, a person of ordinary skill in the art would not be motivated to introduce into the placentas allegedly disclosed by MacLaren a cell that is neither maternal nor fetal in origin. Therefore, MacLaren does not render claims 54 and 68 obvious.

Applicant respectfully requests that the Examiner withdraw the rejections of claims 54 and 68 under 35 U.S.C. §§ 102(b) and 103(a) on this basis.

The Examiner further rejects claims 54, 60-65 and 68 under 35 U.S.C. § 103(a) as obvious over MacLaren in view of Sanders et al., United States Patent No. 3,862,002 ("Sanders"), and Stromberg et al., *Methods in Cell Biol.* 21B:227-252 (1980) ("Stromberg"). Applicants traverse, because (1) the combination of references fails to teach or suggest each and every limitation of the claims, (2) there is no motivation to combine the references, and (3) there is no reasonable expectation of practicing the claimed invention through combination of the three references' alleged disclosures.

The combination of cited references fails to teach or suggest a placenta comprising a cell which is neither fetal nor maternal in origin. As explained above, MacLaren allegedly teaches only a post-partum placenta which contains no exogenous non-maternal, non-fetal cell. Neither Stromberg nor Sanders remedies this deficiency, because neither teaches a placenta comprising such a cell or suggests placing such a cell into a placenta. Therefore, the combination of MacLaren, Stromberg and Sanders fails to teach or suggest all limitations of claims 54, 60-65 and 68, and the combination does not render these claims obvious.

Moreover, there is no motivation to combine the references. The Examiner contends that Stromberg teaches that "the human placenta is a gift from nature for biological investigation in [a] wide variety of subjects . . ." Office Action, page 14. This statement, offered presumably to show motivation to combine the references, is merely an invitation to experiment, and does not suggest combining the cited references to achieve the recited placenta. MacLaren, as noted above, purportedly teaches a post-partum mammalian placenta that lacks any additional non-maternal, non-fetal cells. One of ordinary skill in the art would not be motivated to combine the alleged disclosure of MacLaren with the alleged disclosures of Stromberg and/or Sanders, neither of which teaches a placenta comprising another cell, to produce the claimed placenta comprising a cell that is neither fetal nor maternal in origin.

Moreover, because the combination of references fails to teach or suggest such a placenta, a person of ordinary skill in the art would have no reasonable expectation of success in combining the three cited references.

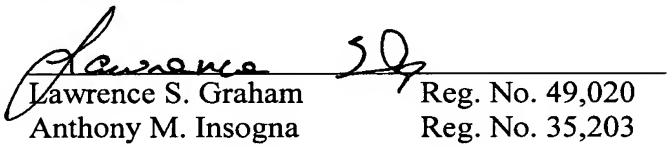
Thus, the combination of MacLaren, Sanders and Stromberg does not render claims 54, 60-65 and 68 obvious. Applicant requests that the Examiner withdraw the rejection of these claims on this basis.

Conclusion

For the reasons provided above, the claims as amended, and new claims, should now be in condition for allowance, and early notice of the same is earnestly solicited. No new search of the prior art is required to assess patentabilty of the claims. Applicants believe that no fee is due for this Amendment, beyond that authorized in the accompanying documents. However, if a fee should be deemed due, please charge such fee to Jones Day deposit account no. 503013.

Respectfully submitted,

Date April 19, 2005



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